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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

RE: Docket Number 98D-0265
Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act

Dear Sir or Madam:

Teva Pharmaceuticals USA (Teva) has the following remarks with regard to comments submitted to FDA's June 1998 guidance implementing Section 505A of the Federal Food, Drug, and Cosmetic Act by the following entities on the dates indicated:

Glaxo Wellcome, Inc. (Glaxo) - September 25, 1998
Wyeth-Ayerst Research (Wyeth) - October 2, 1998
American Academy of Pediatrics (AAP) - October 5, 1998

As we stated in our September 17, 1998 comment to this docket, Teva fully supports the concept of providing incentives for research to improve the health care of children. And, as we also stated in our prior comment, we believe the FDA should consider some changes to the June 1998 guidance in order to insure that its intent, i.e., to optimize the use of drug products in the pediatric population, is not compromised by the financial self-interest of brand-name companies whose clear objective is the receipt of extended protection against competition in the market place. It is from this position that we offer the following comments.

The Glaxo Letter

The thrust of Glaxo's comments, if distilled to their simplest form, is to thwart competition from generic companies while advancing Glaxo's own corporate goals in the implementation of Section 505A. Glaxo claims that the requirement for a Written Request prior to the performance of pediatric studies penalizes sponsors who pro-actively performed such studies prior to the publication date of the guidance, while rewarding sponsors who withheld data until the issuance of the guidance and the

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receipt of a Written Request. The basic purpose of Section 505A, however, is to provide an incentive to generate pediatric drug data, and an "incentive," by definition, is something that incites to action. The truth of the matter is that companies that have demonstrated a commitment to pediatric drug development by performing studies of their own volition may deserve commendation already obtained, but clearly do not require or deserve an incentive. Conversely, those who withhold data are behaving unethically since they are knowingly and wilfully placing corporate profits over the health of children.

Since exclusivity is an incentive that is not without a price (increased cost of drugs to the public), corporate strategies that result in undeserved exclusivity undermine the intent of both Hatch/Waxman and FDAMA. Even with this in mind, FDA has attempted to satisfy the self-interest of brand-name companies by giving priority to drugs whose existing patent or exclusivity protection expires on or before March 31, 1999, rather than to those drugs which would most benefit the pediatric population. This has been noted by Congress in recent hearings on the issue. In addition, FDA has permitted studies submitted to an NDA after November 20, 1997 and before July 1, 1998 to be considered responsive to a Written Request and therefore to potentially support exclusivity.[1] Hence, contrary to the intent of Congress to provide incentives, retrospective exclusivity—a non-incentive based provision since the work has already been performed—is being permitted. Nonetheless, companies like Glaxo still feel they have not been given adequate incentive and should be rewarded for work they chose to initiate on their own.

Glaxo also proposes that the authority to issue Written Requests should be granted to the Review Divisions since sponsors have a better idea of how the Review Divisions would view planned pediatric studies. Additionally, in Glaxo's view, Review Divisions would be more likely to support the sponsors' proposals and ultimately to issue Written Requests in line with those proposals. Again, self-interest is overriding the intent of Section 505A here. Clearly, sponsors can exert more influence on and have more interaction with Review Divisions than with Office Directors, but Review Divisions are less knowledgeable about the long-term impact of their decisions on the general public. Review Divisions cannot appreciate the "big picture" of children's health care as well as Office Directors, who have oversight of many and varied therapeutic drug classes. A Review Division could not adequately prioritize, for example, the benefit of studies on a cardiovascular drug relative to a CNS drug. As set forth in FDA's "List of Approved Drug Products for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population," priority should be given only to those drugs which would be a <u>significant</u> improvement compared to <u>marketed products</u> labeled for pediatric use, drugs widely used in the pediatric population, or drugs

[1] Manual of Policies and Procedures 6020.6, Center for Drug Evaluation and Research, p. 2.

in a class or for an indication for which additional options for the pediatric population are needed. Office Directors can also better assess the impact of brand exclusivity on the whole patient population as well as on other vulnerable sub-segments such as the elderly. This overall benefit/risk assessment is essential to the appropriate implementation of the statute in order to insure that the maximum benefit is obtained at the minimum risk and cost.

The Wyeth Letter

Wyeth is apparently not satisfied with only six months of additional market monopoly. It suggests that FDA permit sponsors to submit pediatric study reports up until the day the existing market exclusivity expires and then grant 60 - 90 days of additional market exclusivity while FDA reviews the study reports. Wyeth does not stipulate whether this 60 - 90 days would be counted as part of the six month extension or would be in addition to it. However, Wyeth's request is contrary to the intent of Congress in several ways: (1) The 60 - 90 days exclusivity provides an incentive for sponsors to withhold data until patent/exclusivity expiry, (2) A sponsor could gain 60 - 90 days additional market protection even if it submits a completely sub-standard pediatric study report, and (3) The total extension of market protection could be as much as nine months.

Wyeth proposes that studies performed and submitted before FDA issues a Written Request should be allowed to be "re-submitted" under the pediatric exclusivity provisions. As stated previously in this document, this approach is contrary to the definition of "incentive" as an enticement to engage in some future activity, and is therefore contrary to Congressional intent. Further, withdrawing and re-submitting data can amount to withholding data, which may be unethical.

Wyeth further proposes that the guidance not require sponsors to notify FDA of any time frames relevant to the conduct and completion of pediatric studies or of any changes in these time frames. The guidance required this notification process, however, in order to prevent abuses of the exclusivity provisions such as the process proposed by Wyeth in its first comment, i.e., 60 - 90 days additional exclusivity while FDA reviews a study report submitted at the latest possible time. This requirement should be maintained.

Lastly, Wyeth commends FDA for the broad provision that pediatric exclusivity will attach to any exclusivity or patent protection for any drug product containing the same active moiety as the drug studied, and for which the party submitting the study(ies) holds the approved NDA. While it is

obvious why this section has Wyeth's endorsement, in actuality the blanket assignment of exclusivity to dosage forms and doses not studied obliterates the incentive for further study and, with it, the chance of accurate label instructions for the use of these products in children.

The AAP Letter

In contrast to both Glaxo and Wyeth, it is clear that the AAP has the highest standards and best interests of the practice of pediatric medicine and the well-being of children at the heart of its comments. AAP's commitment to the advancement of pediatric medicine is evident in its suggestions, which recognize that pediatricians and children have nothing to gain and potentially a great deal to lose by the inappropriate award of pediatric exclusivity. For emphasis we have re-stated below the comments of the AAP in their October 5, 1998 letter, which we fully endorse:

- Representative John Dingell (D-MI) is quoted from his remarks on the House floor during consideration of the conference report on the Food and Drug Administration Modernization Act: "Market incentives are included in the bill to encourage pediatric studies, so that labeling of these products will be useful to pediatricians." Accordingly, all new information derived from these studies that would enhance the medical care of children should be incorporated into labeling within established time frames.

- A single Written Request should be issued that encompasses both labeled and off-label uses that require additional study. The single Written Request should also encompass all pediatric sub-populations that may benefit. In this way sponsors could not exclude sub-populations that are difficult or expensive to study and/or those with small market potential and still be granted pediatric exclusivity.

- FDA should examine, on a case-by-case basis, the need to reformulate a drug product for the pediatric population and include this as part of the requirements of the Written Request.

- FDA should establish a standard for what the guidance refers to as "completion of the study." The mere completion of a study should not qualify a sponsor for exclusivity. The study data should be analyzed and interpreted by the sponsor and then judged to be acceptable by FDA prior to the granting of exclusivity.

- FDA should develop a tracking system for all the drugs on the "List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population." This tracking system would monitor the progress made under the current

guidance toward fulfilling the objectives of Section 505A. It would set forth, among other things, how many actual labeling revisions for pediatric use were made, how many Written Requests were rejected by sponsors and why, the number of drugs granted exclusivity, and how many drugs were added to the list.

In summary, while the concept of pediatric exclusivity is worthy, the potential for abuse and misuse of the provisions of the guidance are very real. Teva urges FDA to examine this potential and to implement modifications to the guidance to safeguard the original intent of the law. It is the consumer who will ultimately bear the cost burden of extended exclusivity. It is incumbent upon FDA to ensure that there is a commensurate advancement in the quality of health care for children to offset this burden. Plainly, moreover, the view of an institution whose purpose is to serve the health needs of children, such as the AAP, should be given precedence over the self-serving comments of branded companies whose primary goal appears to be to extract the maximum additional monopoly protection from a law whose true intent was to benefit children's health.

Respectfully submitted,

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